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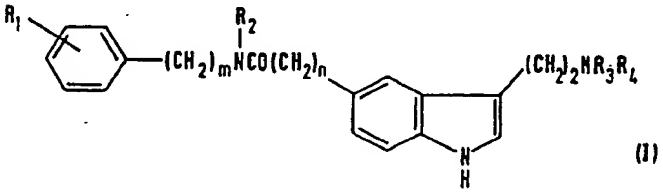
(54) Indole derivatives

(57) Compounds of formula (I):



(I)

[wherein
R_1 is R_5R_6N-, $R_5O_2C(CH_2)_p-$, $R_5R_6NCO(CH_2)_p-$, $R_5CONH(CH_2)_p-$, $R_5R_6NSO_2(CH_2)_p-$ or $R_7SO_2NH(CH_2)_p-$
(where R_5 and R_6 are independently hydrogen or C_{1-3} alkyl, or R_5 and R_6 together with the nitrogen atom to which they are attached form a saturated monocyclic 5- to 7-membered ring; R_7 is C_{1-3} alkyl and p is zero or one); R_2 is hydrogen or C_{1-3} alkyl; R_3 and R_4 are independently hydrogen, C_{1-3} alkyl, or a 2-propenyl group;
m is zero or an integer from 1 to 4; and
n is zero or one (with the proviso that m and n are not both zero)] and
physiologically acceptable salts and solvates (e.g. hydrates) thereof, have potent and selective vasoconstrictor activity and are indicated as useful for the *treatment of migraine*.

The compounds may be formulated as pharmaceutical compositions with pharmaceutically acceptable carriers or excipients for administration by any suitable means. Various methods for the preparation of the compounds are disclosed.

GB 2 191 488 A

SPECIFICATION

Indole derivatives

This invention relates to indole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use, in particular to compounds and compositions of use in the treatment of migraine.

The pain of migraine is associated with excessive dilatation of the cranial vasculature, and known treatments for migraine include the administration of compounds having vasoconstrictor properties, such as ergotamine. However, ergotamine is a non-selective vasoconstrictor which constricts blood vessels throughout the body and has undesirable and dangerous side effects. Migraine may also be treated by administering an analgesic, usually in combination with an antiemetic, but such treatments are of limited value.

There is thus a need for a safe and effective drug for the treatment of migraine, which can be used either prophylactically or to alleviate an established headache, and a compound having a selective vasoconstrictor activity would fulfil such a role.

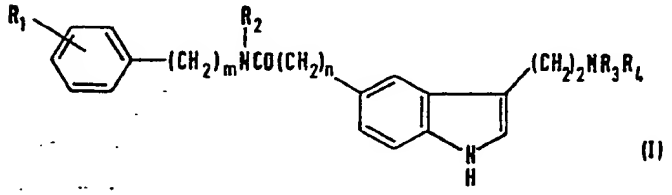
A number of classes of compounds having selective vasoconstrictor activity have been described.

Thus, UK Patent Specification No. 2035310 discloses a wide variety of 5-carboxamido and thioamido substituted indole derivatives. The compounds are described as having antihypertensive activity and it is disclosed that certain compounds of the invention are also potentially useful for the treatment of migraine.

UK Patent Specification No. 2082175 describes various 5-acetamido and 5-thioamido substituted indole derivatives having selective vasoconstrictor activity. As indicated in the UK Patent Specification No. 2082175, these compounds selectively constrict the carotid arterial bed of the anaesthetised dog and are thus potentially useful for the treatment of migraine.

We have now found a novel group of indole derivatives having potent and selective vasoconstrictor activity.

Thus, the present invention provides an indole of the general formula (I):



(I)

wherein

R_1 represents a group R_5R_6N-, a group $R_5O_2C(CH_2)_p-$, a group $R_5R_6NCO(CH_2)_p-$, a group $R_5CONH(CH_2)_p-$, a group $R_5R_6NSO_2(CH_2)_p-$ or a group $R_7SO_2NH(CH_2)_p-$, (where R_5 and R_6, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group, or R_5 and R_6 together with the nitrogen atom to which they are attached form a saturated monocyclic 5-to 7-membered ring; R_7 represents a C_{1-3} alkyl group and p is zero or one); R_2 represents a hydrogen atom or a C_{1-3} alkyl group; R_3 and R_4 which may be the same or different each represents a hydrogen atom, a C_{1-3} alkyl group, or a 2-propenyl group;
m is zero or an integer from 1 to 4 ; and
n is zero or one (with the proviso that m and n are not both zero); and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

The invention includes within its scope all optical isomers of compounds of formula (I) and their mixtures including the racemic mixtures thereof. All geometric isomers of compounds of general formula (I) are also included within the scope of the invention.

In the compounds of formula (I) it will be appreciated that the substituent R_1 may be in the ortho, meta or para positions.

Referring to the general formula (I), the alkyl groups may be straight chain or branched chain alkyl groups, such as methyl, ethyl or isopropyl groups. The substituent R_1 may be in the ortho, meta or para position.

Preferred compounds represented by general formula (I) are those in which R_2, R_3, R_4, m and n have the meanings defined above and R_1 represents a group R_5R_6N-, $R_5O_2C(CH_2)_p-$, $R_5R_6NCO(CH_2)_p-$, $R_5CONH(CH_2)_p-$, $R_5R_6NSO_2(CH_2)_p-$ or a group $R_7SO_2NH(CH_2)_p$ where R_5 and R_6, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group and R_7 and p have the meanings defined above.

A preferred class of compounds represented by the general formula (I) is that wherein R_2 represents a hydrogen atom or a methyl group.

In the compounds of general formula (I), m may be zero or an integer from 1 to 4 but is preferably 2.

Another preferred class of compounds of general formula (I) is that wherein R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group, for example a methyl or ethyl group.

In the compounds of general formula (I) wherein R_1 represents a R_5R_6N-, $R_5O_2C(CH_2)_p-$, $R_5R_6NCO(CH_2)_p-$, $R_5CONH(CH_2)_p-$ or $R_5R_6NSO_2(CH_2)_p-$ group, R_5 and R_6, which may be the same or different, each preferably represents a hydrogen atom or a methyl group. Where R_5 and R_6 together form a saturated monocyclic 5 to 7 membered ring, this will preferably be a pyrrolidino ring.

In the compounds of general formula (I) wherein R_1 represents the group $R_7SO_2NH(CH_2)_p-$, R_7 preferably represents a methyl group.

Suitable substituents R_1 in compounds of general formula (I) include, for example, the groups H_2NCOCH_2-, CH_3SO_2NH-, H_2NCO-, $(CH_3)_2N-$, CH_3O_2C-, pyrrolidino and $CH_3NHSO_2CH_2-$.

The substituent R_1 in compounds of general formula (I) is preferably at the meta or para position.

A particularly preferred group of compounds falling within the scope of general formula (I) is that wherein R_2 represents a hydrogen atom; R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a methyl group; m represents an integer 2; R_1 represents the group H_2NCOCH_2-, CH_3SO_2NH-, CH_3CONH-, H_2NCO-, $(CH_3)_2N-$, CH_3O_2C-, $CH_3NHSO_2CH_2-$ or a pyrrolidino ring; and the substituent R_1 on the phenyl ring is at the meta or para position.

Particularly preferred compounds of general formula (I) falling within this group are those in which R_1 represents the group $(CH_3)_2N-$, CH_3O_2C-, H_2NCOCH_2- or CH_3CONH- and the group R_1 is at the para position.

Preferred compounds according to the invention include :-
3-(2-Aminoethyl)-N-[2-[4-(dimethylamino)phenyl]ethyl]-1*H*-indole-5-carboxamide;
Methyl 4-[2-[[[3-(2-aminoethyl)-1*H*-indol-5-yl]carbonyl]amino]ethyl]benzoate;
and their physiologically acceptable salts and solvates (for example, hydrates) thereof.

Suitable physiologically acceptable salts of the indoles of general formula (I) include acid addition salts formed with inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, nitrates, oxalates, phosphates, tartrates, citrates, fumarates, maleates, succinates, and sulphonates e.g. mesylates. Other salts may be useful in the preparation of compounds of formula (I) e.g. creatinine sulphate adducts.

It will be appreciated that the invention extends to other physiologically acceptable equivalents of the compounds according to the invention, i.e. physiologically acceptable compounds which are converted *in vivo* into the parent compound. Examples of such equivalents include physiologically acceptable, metabolically labile N-acyl derivatives.

Compounds of the invention selectively constrict the carotid arterial bed of the anesthetised dog, whilst having a negligible effect on blood pressure. The selective vasoconstrictor action of compounds of the invention has also been demonstrated *in vitro*.

Compounds of the invention are useful in treating pain resulting from dilatation of the cranial vasculature, in particular migraine and cluster headache.

Accordingly, the invention also provides a pharmaceutical composition adapted for use in human medicine which comprises at least one compound of formula (I) or a physiologically acceptable salt or solvate (e.g. hydrate) thereof and formulated for administration by any convenient route. Such compositions may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-*p*-hydroxybenzoates or sorbic acid). The liquid preparations may also contain conventional buffers, flavouring, colouring and sweetening agents as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formu-

lated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative.

The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents, and/or agents to adjust the tonicity of the solution. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the compounds of the invention for oral, parenteral, buccal or rectal administration to man (of average bodyweight e.g. about 70kg) for the treatment of migraine is 0.1 to 100mg of the active ingredient per unit dose which could be administered, for example, up to 8 times per day, more usually 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

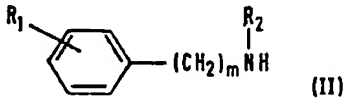
For oral administration a unit dose will preferably contain from 0.5 to 50mg e.g. 2 to 40mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.2 to 5mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 to 2mg of a compound of the invention and each dose administered via capsules or cartridges in an inhaler or insufflator contains 0.2 to 20mg. The overall daily dose by inhalation will be within the range 1mg to 100mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents, such as analgesics, anti-inflammatory agents and anti-nauseants.

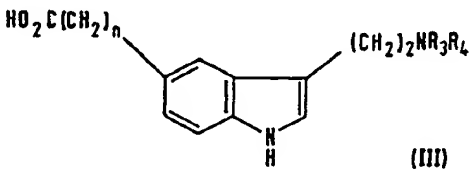
According to another aspect of the invention, compounds of formula (I), and physiologically accepable salts or solvates (e.g. hydrates) thereof, may be prepared by the general methods outlined below. In the following processes, R_1, R_2, R_3, R_4, m and n are as defined for the general formula (I) unless otherwise specified.

According to one general process (A), a compound of general formula (I) may be prepared by condensing an amine of formula (II):



(II)

with an acid of general formula (III):



(III)

or an acylating agent corresponding thereto, or a salt (for example an organic or inorganic acid addition salt such as the hydrochloride, hydrobromide, sulphate or maleate salt, or creatinine sulphate adduct) or a protected derivative thereof.

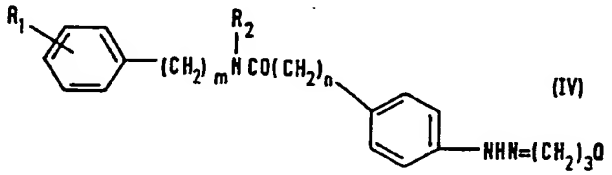
The reaction involving condensation of the amine of formula (II) with the acid of general formula (III) is desirably conducted in the presence of a coupling agent, for example carbonyl diimidazole or a carbodiimide such as N,N'-dicyclohexylcarbodiimide. The condensation reaction

may be carried out in a suitable reaction medium preferably an anhydrous medium, conveniently at a temperature of from −50 to +50°C, preferably −5 to +30°C. Suitable solvents include halogenated hydrocarbons e.g. dichloromethane, nitriles e.g. acetonitrile, amides e.g. N,N-dimethylformamide and ethers e.g. tetrahydrofuran, as well as mixtures of two or more such solvents. The reaction may also be carried out in the absence of a coupling agent in a suitable reaction medium such as a hydrocarbon (e.g. toluene or xylene) conveniently at a temperature of from 50 to 120°C.

Acylating agents corresponding to the acid of general formula (III) which may be employed in the preparation of compounds of formula (I) include acid halides, for example acid chlorides. Such acylating agents may be prepared by reaction of an acid of general formula (III), or a salt or protected derivative thereof, with a halogenating agent such as phosphorus pentachloride, thionyl chloride or oxalyl chloride. Other suitable acylating agents which may be employed in the preparation of compounds of formula (I) include alkyl esters such as the methyl ester, activated esters (e.g. the 2-(1-methylpyridinyl)ester) and mixed anhydrides (e.g. formed with pivaloyl chloride, a sulphonyl halide such as methanesulphonyl chloride or a haloformate, such as a lower alkylhaloformate). Acids of formula (III) may themselves be prepared for example by cyclisation of an appropriate hydrazine compound, in an analogous manner to process (B) described hereinafter.

When an acylating agent corresponding to the acid of general formula (III) is employed the condensation process may be effected in aqueous or non-aqeuous reaction media and conveniently at a temperature of from −70 to +150°C. Thus the condensation reaction using an acid halide, anhydride or activated ester may be effected in a suitable reaction medium such as an amide e.g. N,N-dimethylformamide, an ether e.g. tetrahydrofuran or diethylether, a nitrile e.g. acetonitrile, a halogenated hydrocarbon e.g. dichloromethane, or mixtures thereof, optionally in the presence of a base such as a tertiary amine e.g. triethylamine or pyridine and preferably at a temperature of from −5 to +25°C. The condensation reaction using an alkyl ester may be effected in a suitable reaction medium such as an alcohol e.g. methanol, an amide e.g. dimethylformamide, an ether e.g. tetrahydrofuran or diethylether, or mixtures thereof and conveniently at a temperature of from 0 to 100°C. In some instances, the amine of formula (II) may itself act as the reaction solvent.

According to another general process (B), compounds of formula (I) may be prepared by the cyclisation of a compound of general formula (IV):



(IV)

wherein Q is the group NR_3R_4 (or a protected derivative thereof) or a leaving atom or group such as a halogen atom (e.g. chlorine or bromine) or an acyloxy group (e.g. a carboxylic or sulphonic acyloxy group such as an acetoxy, chloroacetoxy, dichloroacetoxy, trifluoroacetoxy, p-nitrobenzoyloxy, p-toluenesulphonyloxy or methanesulphonyloxy group).

The reaction may conveniently be effected in aqueous or non-aqueous reaction media, and at temperatures of from 20 to 200°C, preferably 50 to 125°C.

Particularly convenient embodiments of the general process (B) are described below.

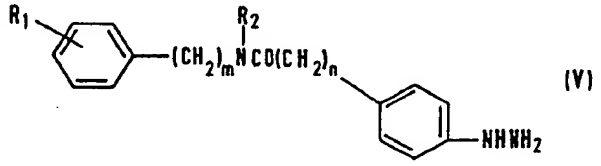
When Q is the group NR_3R_4 (or a protected derivative thereof) the process is desirably carried out in the presence of polyphosphate ester in a reaction medium which may comprise one or more organic solvents, preferably halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, dichlorodifluoromethane, or mixtures thereof. Polyphosphate ester is a mixture of esters which may be prepared from phosphorus pentoxide, diethylether and chloroform according to the method described in 'Reagents for Organic Synthesis', (Fieser and Fieser, John Wiley and Sons 1967).

Alternatively the cyclisation may be carried out in an aqueous or non-aqueous reaction medium, in the presence of an acid catalyst. When an aqueous medium is employed this may be an aqueous organic solvent such as an aqueous alcohol (e.g. methanol, ethanol or isopropanol) or an aqueous ether (e.g. dioxan or tetrahydrofuran) as well as mixtures of such solvents, and the acid catalyst may be for example, an inorganic acid such as concentrated hydrochloric or sulphuric acid or an organic acid, such as acetic acid. (In some cases the acid catalyst may also act as the reaction solvent). In an anhydrous reaction medium, which may comprise one or more ethers (e.g. as previously described) or esters (e.g. ethyl acetate), the acid catalyst will generally be a Lewis acid such as boron trifluoride, zinc chloride or magnesium chloride.

When Q is a leaving group such as a chlorine or bromine atom the reaction may be effected

in an aqueous organic solvent, such as an aqueous alcohol (e.g. methanol, ethanol or isopropanol) or an aqueous ether (e.g. dioxan or tetrahydrofuran) in the absence of an acid catalyst, conveniently at a temperature of from 20 to 200°C, preferably 50 to 125°C. This process results in the formation of a compound of formula (I) wherein R_3 and R_4 are both hydrogen atoms.

According to a particular embodiment of general process (B) compounds of formula (I) may be prepared directly by the reaction of a compound of general formula (V):



(V)

or a salt thereof,
with a compound of formula (VI):

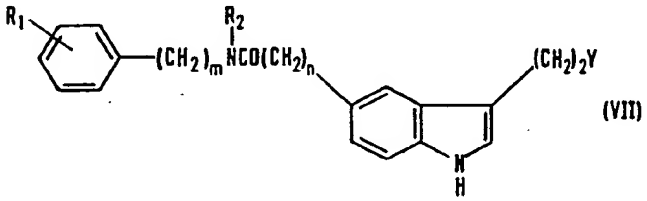
$$OHC(CH_2)_3Q \qquad (VI)$$

(wherein Q is as defined above) or a salt or protected derivative thereof (such as an acetal or ketal e.g. formed with an appropriate alkyl orthoformate or diol, or protected as a bisulphite addition complex) using the appropriate conditions as described above for the cyclisation of compounds of general formula (IV). It will be appreciated that in this embodiment of the cyclisation process (B) a compound of general formula (IV) is formed as an intermediate, and may be reacted *in situ* to form the desired compound of general formula (I).

Compounds of general formula (IV) may, if desired, be isolated as intermediates during the process for the preparation of compounds of formula (I) wherein a compound of formula (V), or a salt or protected derivative thereof, is reacted with a compound of formula (VI), or a salt or protected derivative thereof, in a suitable solvent, such as an aqueous alcohol (e.g. methanol) at a temperature of, for example, 20 to 30°C. If an acetal or ketal of a compound of formula (VI) is used, it may be necessary to carry out the reaction in the presence of an acid (for example, acetic or hydrochloric acid).

Compounds of general formula (V) may be prepared for example from the corresponding nitro compounds, using conventional procedures.

A further general process (C) for preparing compounds of general formula (I) involves reacting a compound of general formula (VII):



(VII)

(wherein Y is a readily displaceable group) or a protected derivative thereof, with an amine of formula R_3R_4NH.

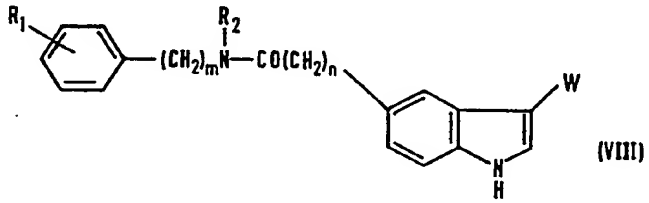
The displacement reaction may conveniently be carried out on those compounds of formula (VII) wherein the substituent group Y is a halogen atom (e.g. chlorine, bromine or iodine) or a group OR_8 where OR_8 is, for example, an acyloxy group which may be derived from a carboxylic or sulphonic acid, such as an acetoxy, chloroacetoxy, dichloroacetoxy, trifluoroacetoxy, p-nitrobenzoyloxy, p-toluenesulphonyloxy or methanesulphonyloxy group.

The displacement reaction may be conveniently effected in an inert organic solvent (optionally in the presence of water), examples of which include alcohols, e.g. ethanol; cyclic ethers, e.g. dioxan or tetrahydrofuran; acylic ethers e.g. diethylether; esters, e.g. ethyl acetate; amides, e.g. N,N-dimethylformamide; and ketones e.g. acetone or methylethyl ketone, at a temperature of from −10 to +150°C, preferably 20 to 50°C.

The compounds of general formula (VII) wherein Y is a halogen atom may be prepared by reacting a hydrazine of general formula (V) with an aldehyde or ketone (or a protected derivative thereof) of formula (VI) in which Q is a halogen atom, in an aqueous alkanol (e.g. methanol) containing an acid (e.g. acetic or hydrochloric acid). Compounds of formula (VII) wherein Y is the group OR_8 may be prepared from the corresponding compound wherein Y is a hydroxyl group by acylation or sulphonylation with the appropriate activated species (e.g. anhydride or sulphonyl

chloride) using conventional techniques. The intermediate alcohol may be prepared by cyclisation of a compound of formula (IV) wherein Q is a hydroxyl group (or a protected derivative thereof) under standard conditions.

Compounds of formula (I) may also be prepared by another general process (D) involving reduction of a compound of general formula (VIII):



(VIII)

(wherein W is a group capable of being reduced to give the required $-(CH_2)_2NR_3R_4$ group or to give a protected derivative of $-(CH_2)_2NR_3R_4$) or a salt or protected derivative thereof.

The required $-(CH_2)_2-$ and $-NR_3R_4$ groups at the 3- position may be formed by reduction steps which take place separately or together in any appropriate manner.

Examples of groups represented by the substituent W include $-(CH_2)_2NO_2$; $-CH=CHNO_2$; $-(CH_2)_2N_3$; $-CH_2CN$; $-CH_2CHO$; $-COCH_2Z$; $-CH_2CH=NOH$; and $-CH(OH)CH_2NR_3R_4$; (wherein Z is an azido group or the group $-NR_3R_4$ or a protected derivative thereof).

Groups which may be reduced to the $-(CH_2)_2-$ moiety at the 3-position include the corresponding unsaturated group and corresponding groups containing a hydroxyl group or a carbonyl function.

Groups which may be reduced to the group $-NR_3R_4$ where R_3 and R_4 are both hydrogen include nitro, azido, hydroxyimino and nitrile groups. In the latter case, reduction yields the group $-CH_2NH_2$ and thus provides a methylene group of the $-(CH_2)_2-$ moiety.

The required $-NR_3R_4$ group wherein R_3 and/or R_4 are other than hydrogen may be prepared by reduction of a nitrile $-CH_2CN$ or an aldehyde $-CH_2CHO$ in the presence of an amine, R_3R_4NH.

A particularly suitable method for preparing a compound of formula (I) wherein R_3 and/or R_4 is other than hydrogen is reductive alkylation of the corresponding compound wherein R_3 and/or R_4 represent hydrogen with an appropriate aldehyde or ketone (e.g. formaldehyde or acetone) in the presence of a suitable reducing agent. In some instances (e.g. for the introduction of the group(s) R_3 and/or R_4 where these represent methyl) the aldehyde (e.g. formaldehyde) may be condensed with the amine and the intermediate thus formed may subsequently be reduced using a suitable reducing agent.

It will be appreciated that the choice of reducing agent and reaction conditions will be dependent on the nature of the group W, as well as the other groups already present on the molecule.

Suitable reducing agents which may be used in the above process for the reduction of compounds of formula (VIII) wherein W represents, for example, the groups $-(CH_2)_2NO_2$, $-CH=CHNO_2$, $-(CH_2)_2N_3$,$-CH_2CN$, $-CH_2CH=NOH$ and $-CH(OH)CH_2NR_3R_4$ include hydrogen in the presence of a metal catalyst, for example Raney Nickel or a noble metal catalyst such as platinum, platinum oxide, palladium, palladium oxide or rhodium, which may be supported, for example, on charcoal, kieselguhr or alumina. In the case of Raney Nickel, hydrazine may also be used as the source of hydrogen. This process may conveniently be carried out in a solvent such as an alcohol e.g. ethanol, an ether, e.g. dioxan or tetrahydrofuran, an amide, e.g. dimethylformamide or an ester e.g. ethyl acetate, and at a temperature of from −10 to +50°C, preferably −5 to +30°C.

The reduction process may also be effected on compounds of formula (VIII) wherein W represents, for example, the groups $-(CH_2)_2NO_2$, $-CH=CHNO_2$, $-(CH_2)_2N_3$, $-CH(OH)CH_2NR_3R_4$ or $-COCH_2Z$ (where Z is as previously defined), using an alkali metal or alkaline earth metal borohydride or cyanoborohydride e.g. sodium or calcium borohydride or cyanoborohydride which process may conveniently be carried out in an alcohol such as propanol or ethanol, or a nitrile such as acetonitrile, and at a temperature of from 10 to 100°C, preferably 50 to 100°C. In some instances the reduction using a borohydride may be carried out in the presence of cobaltous chloride.

Reductive alkylation of a compound of formula (VIII) may be effected using an alkali metal or alkaline earth metal borohydride or cyanoborohydride. The reaction may be effected in an aqueous or non-aqueous reaction medium, conveniently in an alcohol (e.g. methanol or ethanol) or an ether (e.g. dioxan or tetrahydrofuran) optionally in the presence of water. The reaction may conveniently be carried out at a temperature in the range 0 to 100°C, preferably 5 to 50°C.

A particular embodiment of general process (D) includes the reduction of a compound of formula (VIII) wherein W is the group $-CH_2CN$, for example by catalytic reduction with hydrogen

in the presence of a catalyst such as palladium on charcoal or rhodium on alumina, optionally in the presence of an amine HNR_3R_4. The reduction may be effected in a suitable solvent such as an alcohol e.g. methanol or ethanol.

A compound of general formula (I) where R_4 is a hydrogen atom may also be prepared by hydrogenolysis of a corresponding compound wherein R_4 is a benzyl group, e.g. with hydrogen in the presence of a catalyst, e.g. 10% palladium on carbon.

The starting materials or intermediate compounds of formula (VIII) wherein W represents $-(CH_2)_2NO_2$, $-CH=CHNO_2$, $-CH_2CN$ or $-COCH_2Z$ may be prepared by analogous methods to those described in UK Published Patent Application No. 2035310, and 'A Chemistry of Heterocyclic Compounds—Indoles Part II', Chapter VI, edited by W J Houlihan (1972) Wiley Interscience, New York.

Compounds of formula (VIII), wherein W is the group $-CH_2CHO$ may be prepared by oxidation (e.g. with Jones' reagent) of a compound of formula (VII) wherein Y is a hydroxyl group. A compound of formula (VIII) wherein W is the group $-CH_2CH=NOH$ may be prepared by treatment of the corresponding aldehyde with hydroxylamine hydrochloride using standard conditions.

The intermediate compound of formula (VIII) wherein W is the group $-(CH_2)_2N_3$ may be prepared from a compound of formula (VII) wherein Y is a halogen atom using standard procedures.

Standard reducing agents such as sodium borohydride may be used to prepare a compound of formula (VIII) wherein W is the group $-CH(OH)CH_2NR_3R_4$ from the corresponding compound of formula (VIII) wherein W is the group $-COCH_2NR_3R_4$.

According to a further general process (E) a compound of formula (I) according to the invention, or a salt or protected derivative thereof, may be converted into another compound of formula (I) using conventional procedures.

For example, a compound of general formula (I) wherein one or more of R_2, R_3 and R_4 are alkyl groups may be prepared from the corresponding compounds of formula (I) wherein one or more of R_2, R_3 and R_4 represent hydrogen atoms, by reaction with a suitable alkylating agent such as a compound of formula R_xL, (where R_x represents the desired R_2, R_3 or R_4 group and L represents a leaving group such as a halogen atom or a tosylate group) or a sulphate $(R_x)_2SO_4$. Thus, the alkylating agent may be for example an alkyl halide (e.g. methyl or ethyl iodide), alkyl tosylate (e.g. methyl tosylate) or dialkylsulphate (e.g. dimethylsulphate).

The alkylation reaction may conveniently be carried out in an inert organic solvent such as an amide (e.g. dimethylformamide), an ether (e.g. tetrahydrofuran) or an aromatic hydrocarbon (e.g. toluene) preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides such as sodium or potassium hydride; alkali metal amides such as sodium amide; alkali metal carbonates such as sodium carbonate; alkali metal alkoxides such as sodium or potassium methoxide, ethoxide or t-butoxide; and tetrabutylammonium fluoride. When an alkyl halide is employed as the alkylating agent the reaction may also be carried out in the presence of an acid scavenging agent such as propylene or ethylene oxide. The reaction may be conveniently effected at a temperature of from −20° to 100°C.

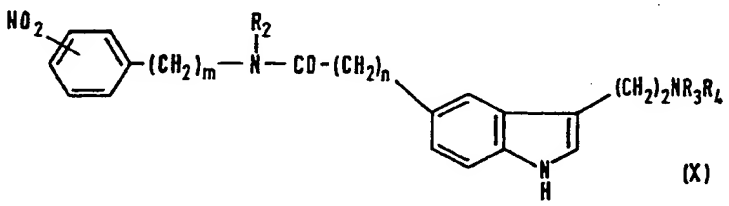
Compounds of formula (I) wherein one or both of R_3 and R_4 represents propenyl may be prepared similarly, using an appropriate compound of formula R_xL or $(R_x)_2SO_4$.

According to another embodiment of general process (E) compounds of general formula (I) wherein R_1 represents a group $R_5CONH(CH_2)_p-$ or a group $R_7SO_2N(CH_2)_p-$ may be prepared by reacting a corresponding compound of general formula (I) wherein R_1 represents $H_2N(CH_2)_p-$ with a reagent serving to introduce the group R_6CO- or R_7SO_2-. Suitable reagents include acids of formula R_5COOH and acylating derivatives thereof, and sulphonylating agents corresponding to acids of formula R_7SO_3H.

Derivatives of the acids R_5COOH and R_7SO_3H which may be employed in this embodiment of general process (E) include acid halides, e.g. carboxylic acid chlorides and sulphonyl chlorides; mixed anhydrides; alkyl esters; and activated esters, e.g. the 2-(1-methylpyridinyl) ester; as described previously for general process (A). The acylation reaction with an acid of formula R_5COOH or an acylating derivative thereof or a sulphonylating agent corresponding to the acid R_7SO_3H may be effected using similar reaction conditions to those described above for general process (A).

According to a further embodiment of general process (E) compounds of general formula (I) wherein R_1 represents a group $R_5R_6NCO(CH_2)_p-$ may be prepared by reacting a corresponding compound of general formula (I) wherein R_1 represents $R_5O_2C(CH_2)_p-$ with an amine R_5R_6NH. The displacement reaction with an amine of formula R_5R_6NH may be effected using similar reaction conditions to those described above for general process (C).

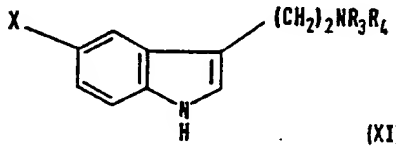
Compounds of general formula (I) wherein R_1 represents H_2N- may also be prepared by a further general process (F) which comprises reduction of a compound of general formula



(X)

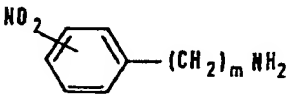
The reduction may be effected for example with hydrogen in the presence of a metal catalyst. Catalysts which may be employed include Raney Nickel, or a noble metal catalyst such as platinum, platinum oxide, palladium, palladium oxide or rhodium, which may be supported, for example on charcoal, kieselguhr or alumina. In the case of Raney Nickel, hydrazine may also be used as the source of hydrogen. The reduction according to general process (F) may conveniently be carried out in a solvent such as an alcohol, e.g. ethanol; an ether, e.g. dioxan or tetrahydrofuran; an amide e.g. dimethylformamide; or an ester e.g. ethyl acetate. The reduction may be effected a temperature in the range −10 to +50°C preferably −5 to +30°C.

Compounds of general formula (X) may be prepared by cyclisation of a corresponding hydrazone, as described in process (B). Alternatively, compounds of formula (X) where n is zero may be prepared by reacting an indole of general formula (XI)



(XI)

(wherein X represents a leaving atom or group such as a halogen atom, e.g. a bromine or iodine atom) with a compound of formula (XII)



(XII)

in the presence of carbon monoxide, and a palladium catalyst.

The reaction may also be effected in the presence of a base. The palladium catalyst may be, for example, a palladium salt derived from an organic acid, e.g. an acetate, or derived from an inorganic acid, e.g. a chloride or bromide; a palladium complex such as a triaryl phosphine complex e.g. a triphenylphosphine or tri(2-methylphenyl) phosphine palladium complex, or finely divided palladium metal, such as palladium on charcoal. A triarylphosphine palladium complex may be generated *in situ* by reacting a palladium salt, e.g. palladium acetate or palladium chloride, with the appropriate triarylphosphine. The reaction may be effected in the presence or absence of a solvent.

Suitable solvents include nitriles e.g. acetonitrile; alcohols e.g. methanol or ethanol; amides e.g. dimethylformamide, N-methylpyrrolidone or hexamethylphosphoramide, and water. The reaction may conveniently be carried out at a temperature of from −10 to 150°C.

According to another general process (G), a compound of general formula (I) according to the invention, or a salt thereof may be prepared by subjecting a protected derivative of general formula (I) or a salt thereof to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the reaction sequence for the preparation of a compound of general formula (I) or a salt thereof it may have been necessary or desirable to protect one or more sensitive groups in the molecule to avoid undesirable side reactions. For example it may be necessary to protect the group NR_3R_4, wherein R_3 and/or R_4 represents hydrogen, by protonation or with a group easily removable at the end of the reaction sequence. Such groups may include, for example, aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl; or acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl or phthaloyl.

In some cases, it may also be desirable to protect the indole nitrogen with, for example, an aralkyl group such as benzyl.

Subsequent cleavage of the protecting group or groups may be achieved by conventional procedures. Thus an aralkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal) or sodium and liquid ammonia; an acyl group

such as N-benzyloxycarbonyl may be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation. The phthaloyl group may be removed by hydrazinolysis (e.g. by treatment with hydrazine hydrate) or by treatment with a primary amine (e.g. methylamine).

As will be appreciated, in some of the general processes (A) to (F) described previously it may be necessary or desirable to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the previously described processes (A) to (F).

Thus, according to a further aspect of the invention, the following reactions in any appropriate sequence may if necessary and/or desired be carried out subsequent to any of the processes (A) to (F):

(i) removal of any protecting groups; and

(ii) conversion of a compound of general formula (I) or a salt thereof into a physiologicIly acceptable salt or solvate (e.g. hydrate) thereof.

Where it is desired to isolate a compound of the invention as a salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I), with an appropriate acid, preferably with an equivalent amount, or with creatinine sulphate in a suitable solvent (e.g. aqueous ethanol).

The starting materials or intermediate compounds for the preparation of the compounds according to this invention may be prepared by analogous methods to those described in UK Patent Specification No. 2035310.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. Thus, for example, the required group at the 5-position may be introduced before or after cyclisation to form the indole nucleus. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following Examples. All temperatures are in °C.

Chromatography was carried out either in the conventional manner using silica gel (Merck (RTM), Kieselgel 60, Art. 7734) or by flash chromatography on silica (Merck 9385) and thin layer chromatography (t.l.c.) on silica (Macherly-Nagel, Polygram) except where otherwise indicated.

Intermediate 1

3-[2-(Dimethylamino)ethyl]-N-[2-(4-nitrophenyl)ethyl]-1H-indole-5-carboxamide

A solution of 5-iodo-N,N-dimethyl-1H-indole-3-ethanamine (100mg), *p*-nitrophenethylamine (80mg), tributylamine (0.3ml) and dichlorobis(triphenylphosphine)palladium (II) (24mg) in dry acetonitrile (5ml) under an atmosphere of carbon monoxide was stirred at reflux for 3.5h and at room temperature overnight (16h). The solvent was removed under reduced pressure in the presence of silica gel (Merck 9385). The impregnated silica was applied as a plug to a silica column (Merck 9385) and elution with dichloromethane-ethanol-ammonia (75:8:1), gave the *title compound* as an oil (47mg).

T.l.c. Silica Dichloromethane-ethanol-aqueous ammonia (75:8:1) Rf 0.19 (major) detection u.v., IPA $KMnO_4$.

Intermediate 2

3-[2-(Dimethylamino)ethyl]-1H-indole-5-acetic acid

A suspension of 3-[2-(dimethylamino)ethyl]-1*H*-indole-5-carbonitrile oxalate (5.6g) in 2N sodium hydroxide (80ml) was heated at 80° for 4h. The reaction mixture was neutralised by dropwise addition of conc. hydrochloric acid to pH 7 and the reaction mixture was evaporated *in vacuo*. The residue was extracted with a mixture of methanol-chloroform (1:10), filtered and concentrated *in vacuo* to give a foam (4.0g).

Analysis Found: C,66.1; H,8.0; N,10.3;
$C_{14}H_{18}N_2O_2.0.2H_2O.0.3C_2H_6O$ requires : C,66.5; H,7.7; N,10.6%.
H_2O Assay contains 1.5% H_2O w/w≡0.2mol H_2O.

Example 1

N-[2-(4-Aminophenyl)ethyl]-3-[2-(dimethylamino)ethyl]-1H-indole-5-carboxamide

A suspension of 10% PdO/C (34mg of a 50% paste with H_2O) in absolute ethanol (10ml) was stirred under an atmosphere of hydrogen at room temperature and pressure for 0.5h. A solution of Intermediate 1 (98mg) in ethanol (7ml) was added and the mixture stirred for 4h. After

removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure to give an oil (ca 100mg) which was purified by column chromatography on silica gel (Merck Art 9385). Elution with isopropylalcohol-diethylether-water-aqueous ammonia (20:20:8:1) afforded the *title compound* as a foam (50mg).

T.l.c. Silica-isopropyl alcohol-ether-water-ammonia (20:20:8:1) Rf 0.30 detection u.v., IPA. N.m.r. δ (DMSO-d_6) includes δ 2.30 (6-H,s,N*Me*$_2$); 2.60 (2H, brt, $-CH_2$ NMe$_2$); 2.70 (2H, brt, PhCH_2–); 2.90 (2H, brt, $-CH_2$NMe$_2$); 4.86 (brs, NH_2); 8.38 (1H, brt, N*H*CO) and 11.04 (1H brs indole N*H*).

Example 2

N-[2-[4-(Acetylamino)phenyl]ethyl]-3-[2-(dimethylamino)ethyl)1H-indole-5-carboxamide

Acetyl chloride (0.32ml) was added dropwise over 10 min to a stirred solution of the product of Example 1 (1.6g) in pyridine (10ml) at 0° under an atmosphere of nitrogen. The solution was allowed to warm to room temperature and stirring was continued for 17h. The reaction was quenched by addition of ice and the resultant solution was stirred for 0.5h. The solvent was removed under reduced pressure (last traces of water azeotroped with toluene) and the residue dissolved in methanol (20ml). Concentration of the solution *in vacuo* in the presence of silica gel (Merck Art 7734) afforded a powder which was applied as a plug to a silica column (Merck Art 9385). Elution with dichloromethane-ethanol-aqueous ammonia (50:8:1) gave the *title compound* as a foam (634mg), which was further purified by HPLC to afford the *title compound* as a foam (174mg).

T.l.c. Silica Dichloromethane-ethanol-aqueous ammonia (25:8:1), Rf 0.38 detection u.v., IPA.

Analysis found C,66.9;H,7.2;N,13.2
$C_{23}H_{28}N_4O_2$.0.3 C_2H_6O.0.8H_2O requires C,67.4;H,7.5;N,13.3%

Example 3

3-[2-(Dimethylamino)ethyl]-N-[2-[4-[(methylsulphonyl)amino]phenyl]ethyl]-1H-indole-5-carboxamide

To a cold (ca 10°) stirred solution of the product of Example 1 (694mg) in pyridine (15ml) was added methanesulphonyl chloride (0.28ml) under an atmosphere of nitrogen. Stirring was continued at room temperature for 26h. The solvent was removed *in vacuo* and the residue dissolved in ethanol (ca 20ml). Water (ca 10ml) was added to the solution, followed by solid potassium carbonate until two layers were observed. The aqueous phase was extracted with ethanol (2 × 10ml) and then the combined organic phases were concentrated under reduced pressure to afford an oil (ca 1.5g). Purification by column chromatography on deactivated alumina employing isopropylalcohol-diethylether-water-aqueous ammonia (65:120:16:2) as eluent gave impure *title compound* as an oil (364mg) and pure *title compound* as an oil which, on trituration with dry ether, afforded a solid (150mg) m.p. 106–109° (dec).

T.l.c. alumina isopropylalcohol-diethylether-water-ammonia (65:120:16:2) Rf 0.7 detection u.v., IPA.

Analysis found C,58.6;H,6.7;N,12.0
$C_{22}H_{28}O_3S$.0.5C_2H_6O.0.95 H_2O requires C,59.0;H,7.0;N,12.0%

Example 4

Methyl 4-[2-[[[3-(2-aminoethyl)-1H-indol-5-yl]carbonyl]amino]ethyl]benzoate hemisuccinate hydrate (4:2:3)

(i) *Methyl 4-[2-[[[3-[2-[[(phenylmethoxy)carbonyl]amino]ethyl]-1H-indole-5-yl]carbonyl]amino]ethyl]-benzoate*

A solution of 3-[2-[[(phenylmethoxy)carbonyl]amino]ethyl]-1*H*-indole-5-carboxylic acid was treated with 1,1′-carbonyldiimidazole (0.324g) and stirred at room temperature for 2h. (Solution A). A suspension of methyl 4-(2-aminoethyl)benzoate hydrochloride (0.435g) in anhydrous tetrahydrofuran (20ml) was treated with triethylamine (0.28ml) and stirred at room temperature for 1 h. (suspension B).

Suspension (B) was added to solution (A) and stirred at room temperature for 48h. The mixture was filtered and the filtrate evaporated under reduced pressure to afford a gum (*ca* 1.3g) which was chromatographed on silica gel (Merck 7734) and eluted with isopropyl acetate. The product, which separated from the appropriate fractions as crystals, was collected and dried to present the *title compound* (0.34g) m.p. 151–153°.

(ii) *Methyl 4-[2-[[[3-(2-aminoethyl)-1H-indol-5-yl]carbonyl]amino]ethyl]benzoate hemisuccinate hydrate (4:2:3)*

A suspension of 10% palladium oxide on carbon (0.35g of a 50% paste with water) in ethanol was pre-reduced by stirring under an atmosphere of hydrogen for 0.5h. A solution of the product of stage (i) (0.333g) in ethanol (25ml) was added to the catalyst suspension and the

mixture was stirred under an atmosphere of hydrogen for 0.75h, until hydrogen uptake ceased (18ml). The catalyst and solvent were removed by filtration and rotary evaporation respectively to afford the free base as a gum (0.22g). The free base (0.22g) in hot isopropanol (2ml) was treated with hot solution of succinic acid (0.037g) in hot isopropanol (2ml). After removal of the solvent (by evaporation under reduced pressure), the residue was triturated with anhydrous ether to present the *title compound* as a powder (0.225g) m.p. 170–5°.
T.l.c. Silica, dichloromethane/ethanol/ammonium hydroxide (35/8/1) Rf 0.4 Detection u.v./IPA

Assay found C,63.0;H,6.05;N,8.99
$C_{21}H_{23}N_3O_3.O.5C_4H_6O_4.O.75H_2O$ requires C,63.07;H,6.33;N,9.59%

Example 5
3-(2-Aminoethyl)-N-[2-[4-(dimethylamino)phenyl]ethyl]-1H-indole-5-carboxamide dihydrochloride
(i) *Phenylmethyl [2-[5-[[2-(4-dimethylaminophenyl)ethyl]amino]carbonyl]-1H-indol-3-yl)ethyl]carbamate hemihydrate*
A solution of 3-[2-[[(phenylmethoxy)carbonyl]amino]ethyl]-1*H*-indole-5-carboxylic acid (1.69g) in anhydrous tetrahydrofuran (25ml) was treated with N,N'-carbonyldiimidazole (0.89g) and heated under reflux with stirring for 1h. A solution of 2-(4-dimethylaminophenyl)ethylamine (0.82g) in anhydrous tetrahydrofuran (10ml) was added to the solution and the mixture was stirred at room temperature for 20h. The solution was evaporated to dryness, under reduced pressure, and the residue mixed with water (150ml) and extracted with ethyl acetate (4×40ml). The combined organic extracts were washed with 8% aqueous sodium bicarbonate solution (3×30ml), dried ($MgSO_4$) and evaporated to yield a gum (2.5g). This material was chromatographed on silica gel (200g, Merck 7734) eluted with isopropyl acetate/petroleum ether (b.p. 60–80°) (1:1) followed by isopropyl acetate. Evaporation of the appropriate fractions afforded a solid (2.3g), which was triturated with anhydrous ether to present the *title compound* as a powder (1.86g) m.p. 139–142°. T.l.c. Silica, dichloromethane/ethanol/0.88 ammonium hydroxide (100:8:1) Rf 0.45 Detection: u.v., IPA.

(ii) *3-(2-Aminoethyl)-N-[2-[4-(dimethylamino)phenyl]ethyl]-1H-indole-5-carboxamide dihydrochloride*
A suspension of 10% palladium oxide on carbon (1.0g of a 50% paste of water) in ethanol (50ml) was pre-reduced by stirring in an atmosphere of hydrogen for 0.5h. The product of stage (i) (1.0g) in ethanol (100ml) was added to the pre-reduced catalyst and the mixture stirred under hydrogn for 1.5h, until uptake of hydrogen ceased (60ml). The catalyst and solvent were removed, by filtration and rotary evaporation respectively, to yield a gum (0.9g), which was chromatographed on a column of silica gel (100g of Merck 7734) eluted with dichloromethane/ethanol/0.88 ammonium hydroxide (50/8/1). Evaporation of the appropriate fractions produced the *title compound* free base as a gum (0.65g). This material (0.65g) was dissolved in hot ethanol (20ml) treated with excess ethereal hydrogen chloride and diluted with ethyl acetate (20ml). The solution was concentrated until cloudy and allowed to cool whereupon a solid crystallised. After collecting the solid by filtration, it was washed with ethyl acetate (10ml) and dried to give the *title compound* as a powder (0.415g) m.p. 210–212°.
T.l.c. Silica, dichloromethane/ethanol/0.88 ammonium hydroxide (25/8/1) Rf 0.45. Detection, u.v. IPA.

Analysis found: C,55.83;H,6.34;N,12.01;Cl,18.64.
$C_{21}H_{26}N_4O.2HCl.O.6H_2O.O.4HCl$ requires C,56.20;H,6.65;N,12.48;Cl,18.95%

Example 6
3-(2-Aminoethyl)-N-[[4-(1-pyrrolidinyl)phenyl]methyl]-1H-indole-5-carboxamide hemisuccinate
(i) *Phenylmethyl [2-[5-[[[4-(1-pyrrolidinyl)phenyl]methyl]amino]carbonyl]-1H-indol-3-yl]ethyl]carbamate*
A solution of 3-[2-[[(phenylmethoxy)carbonyl]amino]ethyl]-1*H*-indole-5-carboxylic acid (1.69g) in anhydrous tetrahydrofuran (25ml) was treated with 1,1-carbonyldiimidazole (0.89g) and heated under reflux for 1h. A solution of 4-(1-pyrrolidinyl)phenylmethylamine (0.88g) in anhydrous tetrahydrofuran (10ml) was added and the resultant solution stirred at room temperature for 48h. The mixture was evaporated to dryness under reduced pressure to give a foam (2.4g) which was purified by chromatography eluting with petroleum ether (b.p. 60–80°) and petroleum ether (b.p. 60–80°)/isopropyl acetate (1:1). Evaporation of the appropriate fractions gave the *title compound* as a powder (0.85g) m.p. 154–157°.

(ii) *3-(2-Aminoethyl)-N-[[4-(1-pyrrolidinyl)phenyl]methyl]-1H-indole-5-carboxamide hemisuccinate*
A suspension of 10% palladium oxide on carbon (0.8g of a 50% paste with water) in ethanol (25ml) was stirred under an atmosphere of hydrogen for ½h. A solution of the product of Stage (i) (0.75g) in ethanol (100ml) was added to the pre-reduced catalyst suspension and the resul-

tant mixture was stirred under an atmosphere of hydrogen for 4h. The suspension was filtered and the filtrate was evaporated under reduced pressure to give a gum (0.35g) which was chromatographed on a column of silica eluted with dichloromethane/ethanol/0.88 ammonium hydroxide mixtures (200/8/1–25/8/1). Evaporation of the appropriate fractions gave the *title compound* free base as a gum which solidified to a solid (0.079g). The free base (0.079g) was dissolved in a hot mixture of isopropanol (2ml) and methanol (3ml) and was treated with a hot solution of succinic acid (0.0134g) in isopropanol (2ml). Concentration and subsequent cooling of the solution caused the *title salt* to crystallise as a solid (0.056g) m.p. 234–8°

Assay Found: C,67.99; H,7.08; N, 13.03;
$C_{22}H_{26}N_4O.C_2H_3O_2$ requires : C,68.39; H,6.93; N, 13.29%.

Example 7

N-[2-[4-(2-Amino-2-oxoethyl)phenyl]ethyl]-3-[2-(dimethylamino)ethyl]-1H-indole-5-carboxamide oxalate

(i) *4-(Cyanomethyl)benzeneacetic acid*

A suspension of 4-[(aminocarbonyl]benzeneacetic acid (1.58g) in dry 1,4-dioxan (50ml) was cooled to below 15° and treated with dry pyridine (1.3ml) followed by trifluoroacetic acid anhydride (2.31ml). The resultant solution was stirred under a nitrogen atmosphere at below 15° for 1.5h. Water (10ml) was added to the solution and the solvent was removed *in vacuo*. The residue was partitioned between water (100ml) and ethyl acetate (100ml) and the aqueous layer was separated and extracted with ethyl acetate (100ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a solid (approximately 3g) which was purified by flash chromatography. Elution with 1% acetic acid in dichloromethane gave two samples of the *title compound* (200mg) m.p. 116–117°, (500mg) m.p. 115–117° as crystalline solids.

(ii) *4-(Cyanomethyl)benzeneacetamide*

To a stirred, fine suspension of the product of Stage (i) (115mg) in dry tetrahydrofuran was added triethylamine (0.175ml) followed by diphenylphosphoryl azide (0.28ml) under a nitrogen atmosphere at room temperature. A saturated solution of ammonia in dry tetrahydrofuran (10ml) was added to the reaction mixture and stirring continued for 5h. The solvent was removed *in vacuo* and the residue purified by flash chromatography eluting with a 10% solution of acetic acid in dichloromethane to give the *title compound* as a solid (approximately 30mg) m.p. 158–160° (dec.).

(iii) *4-(2-Aminoethyl)benzeneacetamide hydrochloride*

The product of Stage (ii) (136mg) in ethanolic hydrogen chloride (10ml) was hydrogenated over pre-reduced 10% palladium oxide on carbon (150mg of a 50% paste with water) in absolute ethanol (10ml) under one atmosphere of hydrogen at room temperature for 30h. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to give impure *title compound* as a solid (approximately 40mg). The catalyst was washed with hot ethanol (100ml) and the ethanolic solution was concentrated *in vacuo* to give further pure *title compound* as a crystalline solid (133mg).

T.l.c. Silica, Dichloromethane-ethanol-acetic acid (150:8:1), Rf 0.08, detection u.v., IPA

(iv) *N-[2-[4-(2-Amino-2-oxoethyl)phenyl]ethyl]-3-[2-(dimethylamino)ethyl]-1H-indole-5-carboxamide oxalate*

Diphenylphosphorylazide (0.27ml) was added to a stirred suspension of 3-[(2-dimethylamino)-ethyl]-1*H*-indole-5-carboxylic acid (144mg) and the product of Stage (iii) (133mg) in triethylamine (0.2ml) and dry dimethylformamide (10ml) at 0° under an atmosphere of nitrogen. The reaction mixture was slowly warmed to room temperature and stirred for 25.5h. The resultant solution was concentrated *in vacuo* (to approximately 1.5ml) and applied directly to a silica gel column (Merck Art 9385; 2.5cm diam). Elution with dichloromethane-ethanol-aqueous ammonia (25:8:1) gave the free base of the *title compound* as a foam (179mg).

T.l.c. Silica, Dichloromethane-ethanol-aqueous ammonia (25:8:1) Rf 0.31, detection u.v., IPA.

The foam (169mg) was dissolved in absolute ethanol (1ml) and added to a solution of oxalic acid (39mg) in ethanol (0.5ml).

Ether (30ml) was added to the resulting precipitate. The solvent was decanted and the solid was washed with ether (30ml) and dried at room temperature under vacuum for 30h to give the *title compound* as a fine powder (202mg, 97%) m.p. 70–72° (foamed).

Analysis Found: C,60.3; H,6.4; N,10.9.
$C_{23}H_{28}N_4O_2.C_2H_2O_4.0.68\ H_2O$ requires C,60.7; H,6.4; N,11.3%.
H_2O assay : 2.46% H_2O w/w≡0.68mol.

Example 8

3-[2-(Dimethylamino)ethyl]-N-[2-[4-[(methylsulphonyl)amino]phenyl]ethyl]-1H-indole-5-acetamide oxalate

Diphenylphosphorylazide (1.73ml) was added to a cooled (ice bath) solution of Intermediate 2 (1.0g), and N-[4-(2-aminoethyl)phenyl]methanesulphonamide (0.87g) in dimethylformamide (140ml) and triethylamine (1.13ml) and the mixture was stirred for 62h. The resulting solution was evaporated to dryness *in vacuo* and the residue was preadsorbed onto silica (7734, 5g). Purification by flash chromatography eluting with dichloromethane-ethanol-aqueous ammonia (100:8:1) gave the *title compound* free base as an oil (1.0g) which was dissolved in hot ethanol (7ml), and a solution of oxalic acid (0.25g, 2.78×10^{-3}mol) in ethanol (2ml) was added. The solvent was evaporated *in vacuo* to give a foam which was triturated with ether (50ml) to give the *title compound* as a foam (0.92g).
T.l.c. Silica, Dichloromethane-ethanol-aqueous ammonia (50:8:1) Rf 0.5 Det. u.v.+IPA.

Analysis Found: C,54.8; H,6.1; N,9.9.
$C_{23}H_{30}N_4O_3S.C_2H_2O_4.0.7H_2O$ requires C,55.1; H,6.2; N,10.3%.
H_2O analysis found 1.83% H_2O w/w≡0.55mol equiv. H_2O

Example 9

3-[2-(Dimethylamino)ethyl]-N-[4-[[(methylamino)sulphonyl]methyl]phenyl]-1H-indole-5-acetamide oxalate

Trimethylacetylchloride (0.27ml) was added to a cooled (5°) suspension of Intermediate 2 (0.5g) in dichloromethane (100ml) and triethylamine (0.71ml) and the mixture was stirred for 30min. 4-Amino-N-methylbenzenemethanesulphonamide hydrochloride (0.48g) was added and the mixture was stirred overnight. Methanol (50ml) was added to the resulting solution and the mixture was stirred for 10min. The solvents were evaporated *in vacuo* and the residue was preadsorbed onto silica (7734, 5g). Purification by flash chromatography eluting with dichloromethane-ethanol-aqueous ammonia (75:8:1) gave the *title compound* free base as a colourless oil (0.6g) which was dissolved in hot ethanol (20ml) and a solution of oxalic acid (0.13g) in ethanol (3ml) was added. On cooling, the *title compound* crystallised out of solution as a solid (0.59g) m.p. 210–213° (foams).

Analysis Found: C,55.2; H,6.0; N,10.5;
$C_{22}H_{28}N_4O_3S.C_2H_2O_4$ requires C,55.6; H,5.8; N,10.8%.

Example 10

N-[2-[4-(Acetylamino)phenyl]ethyl]-3-[2-(dimethylamino)ethyl]-1H-indole-5-acetamide hydrochloride

(i) *3-[2-(Dimethylamino)ethyl]-N-[2-(4-nitrophenyl)ethyl]-1H-indole-5-acetamide hydrochloride*

Diphenylphosphoryl azide (2.1ml) was added to a cooled (ice-bath) solution of Intermediate 2 (1.2g) and 4-nitrophenethylamine hydrochloride (1.0g) in dimethylformamide (200ml) and triethylamine (1.4ml) and the mixture was stirred for 1h. The solution was allowed to warm to room temperature and then stirring was continued for a further 12h. The resulting solution was evaporated to dryness *in vacuo* and the residue was pre-absorbed onto silica (9385, 3g). Purification by column chromatography (Silica 7747, 125g) eluting with dichloromethane-ethanol-aqueous ammonia (50:8:1) gave the impure *title compound* free base. A second column (Silica 7747, 50g) eluting with dichloromethane-ethanol-aqueous ammonia (100:8:1) gave the pure *title compound* free base as an oil (0.8g), a portion of which (0.20g) was dissolved in a mixture of ethanol (1ml) and isopropanol (8ml). Ethereal hydrogen chloride was added to give pH1. Addition of diethyl ether gave the *title compound* as a foam (0.20g)
T.l.c. Silica, Dichloromethane-ethanol-aqueous ammonia (50:8:1) Rf 0.5 Det. u.v.+IPA.

(ii) *N-[2-[4-(Acetylamino)phenyl]ethyl]-3-[2-(dimethylamino)ethyl]-1H-indole-5-acetamide hydrochloride*

A solution of the free base of the product of Stage (i) (0.5g) in ethanol (35ml) and ethanolic hydrogen chloride (6ml) was hydrogenated at room temperature and atmospheric pressure for 30 min over 10% palladium on charcoal (50% paste with water, 0.5g). The catalyst was filtered off and washed with methanol (20ml). The combined filtrates were evaporated to dryness *in vacuo* and the residue was preadsorbed onto silica (7734, 2g). Purification by chromatography eluting with dichloromethane-ethanol-aqueous ammonia (50:8:1) gave N-[2-(4-aminophenyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-5-acetamide (0.39g). Acetyl chloride (0.087ml) was added to a

solution of this amine (0.37g) and triethylamine (0.17ml) in dichloromethane (40ml) and the mixture was stirred for 30 min. A further quantity of acetyl chloride (0.02ml) was added and stirring was continued for 30 min. Methanol (20ml) was added to the mixture which was then stirred for 10 min. The solution was evaporated to dryness *in vacuo* and the residue was preadsorbed onto silica (7734, 1g). Purification by chromatography eluting with dichloromethane-ethanol-aqueous ammonia (50:8:1) gave the pure *title compound* free base as an oil (0.35g) which was dissolved in a mixture of ethanol (3ml) and isopropanol (10ml). Ethereal hydrogen chloride was added to give pH1, and addition of diethyl ether precipitated the *title compound* as a foam (0.27g).
T.l.c, Silica, Dichloromethane-ethanol-aqueous ammonia (50:8:1) Rf 0.2 Det. u.v.+IPA.

Analysis Found: C,62.4; H,7.2; N,12.1.
$C_{24}H_{30}N_4O_2.HCl.0.9H_2O$ requires C,62.8; H,7.2; N,12.2%.
H_2O Analysis found 3.70% H_2O w/w≡0.9mol equiv. H_2O

Example 11

N-[3-[4-(Aminocarbonyl)phenyl]propyl]-3-[2-(dimethylamino)ethyl]-1H-5-carboxamide oxalate

(i) *3-[2-(Dimethylamino)ethyl]-N-(2-propynyl)-1H-indole-5-carboxamideoxalate*

3-[2-(Dimethylamino)ethyl]-1*H*-indole-5-carboxylic acid (2.0g) was dissolved in a mixture of dry pyridine (130ml) and dry dimethylformamide (20ml) in a nitrogen atmosphere (heating is required to effect complete solution). The solution was cooled in an ice bath, and thionyl chloride (1.25ml) was added dropwise. The mixture was stirred at room temperature for 4h. and t.l.c. on silica (diethylether-isopropylalcohol-water-aqueous ammonia 20:20:8:1) showed incomplete reaction. The reaction mixture was re-cooled in an ice bath further thionyl chloride (0.3ml) was added, followed by propargylamine hydrochloride (2.36g). The resulting solution was stirred at room temperature for 16h. T.l.c. using the same solvent system as before showed some starting material present, and further thionyl chloride (0.3ml) and propargylamine hydrochloride (0.4g) were added. The mixture was stirred at room temperature for 20h. The solvents were evaporated *in vacuo* to give a viscous oil, which was mixed with dichloromethane-ethanol-aqueous ammonia (50:8:1) and applied to a silica column. 'Flash' elution using the same solvent system gave the *title compound* free base 880mg as a foam. A further less pure sample of the *title compound* free base (0.214g) was also obtained. A portion of the *title compound* free base (50mg) was dissolved in methanol (0.5ml) and oxalic acid (16.5mg) was added as a solid. Diethyl ether (10ml) was added to give a gummy precipitate. The large gummy globules were removed using a spatula, and the remaining material was stirred at room temperature for 6h to give a precipitate. The precipitate was removed by filtration, but formed a gum immediately. The gum was dried *in vacuo* at 60° for 10h to give the *title compound* as a foam, 20mg.

Analysis Found: C,59.4; H,62; N,11.2.
$C_{16}H_{19}N_3O.C_2H_2O_4.O.2H_2O$ requires C,59.6; H,5.9; N,11.6%.

(ii) *Methyl 4-[3-[[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]carbonyl]-amino]-2-propynyl]benzoate oxalate*

Methyl 4-iodobenzoate (731mg), the free base of the product of Stage (i) (826mg) and bis(triphenylphosphine)palladium dichloride (63mg) were dissolved in a mixture of diethylamine (50ml) and tetrahydrofuran (50ml). Copper (I) iodide (38mg) was added, and the reaction mixture was stirred at room temperature for 18h. The solvents were evaporated *in vacuo* to give an oil, which was dissolved in dichloromethane-ethanol-aqueous ammonia (75:8:1) and applied to a silica column (Merck Art 9385). 'Flash' elution using the same solvent system gave the *title compound* as a foam, (998mg), a portion of which (104mg) was dissolved in methanol (3.5ml) and a solution of oxalic acid (23mg) in methanol (0.5ml) was added. Diethyl ether (100ml) was added, and the *title compound* was isolated as a solid (97mg), m.p. 163–7°C (dec).

(iii) *Methyl 4-[3-[[[3-[2-(dimethylamino]-1H-indol-5-yl]carbonyl]amino]propyl]benzoate oxalate*

The product of Stage (ii) as the free base (173mg) was dissolved in methanol (40ml) and activated charcoal (150mg) was added. The mixture was heated at reflux for 2h and the charcoal was removed from the hot solution by filtration through cotton wool. The cool (room temperature) filtrate was added to a pre-reduced suspension of 10% palladium oxide-on-carbon (50% aqueous paste, 80mg) in ethanol (40ml). The mixture was hydrogenated at 1 atmosphere of hydrogen for 4h. The catalyst was removed by filtration through 'hyflo' RTM, and the solvent was evaporated *in vacuo* to give a gum which was dissolved in dichloromethane-ethanol-aqueous ammonia (50:8:1) and applied to a silica column (Merck Art 9385). 'Flash' elution using the same solvent system gave the *title compound* free base as a foam, (111mg). A portion of the *title compound* free base (99mg) was dissolved in methanol (3ml), and a solution of oxalic acid (22mg) in methanol (0.5ml) was added. Diethyl ether (50ml) was added to give a suspension,

which was stirred at room temperature for 6h. The *title compound* was isolated by filtration as a gummy solid and was dried *in vacuo* at 60° for 20h to give a foam (94mg).

Analysis	Found:	C,63.0; H,6.6; N,8.7.
$C_{24}H_{29}N_3O_3.C_2H_2O_4$	requires	C,62.8; H,6.3; N,8.5%.

(iv) *N-[3-[4-(Aminocarbonyl)phenyl]propyl]-3-[2-(dimethylamino)ethyl]-1H-indole-5-carboxamide oxalate*

The product of Stage (iii) as the free base (560mg) was dissolved in methanol (30ml) and the solution was saturated with gaseous ammonia. The mixture was heated in an autoclave at 110° for 72h. The solvent was evaporated *in vacuo* to give an oil which was dissolved in dichloromethane-ethanol-aqueous ammonia (50:8:1) and applied to a silica column (Merck Art 9385, 4cm diam.×6in). 'Flash' elution using the same solvent system gave starting material 261mg and the free base of the *title compound*, 218mg, a portion of which (207mg) was dissolved in methanol (2ml) and a solution of oxalic acid (47.5mg, 0.53mmol) in methanol (0.5ml) was added. Diethyl ether (50ml) was added, and the resulting gummy precipitate was stirred at room temperature for 6h to give the *title compound* as a solid, (215mg), m.p. foams 70°, melts 133–143°C.

Analysis	Found:	C,62.0; H,6.6; N,11.2.
$C_{23}H_{28}N_4O_2.C_2H_2O_4$	requires	C,62.2; H,6.3; N,11.6%.

T.l.c. Silica, Dichloromethane-ethanol-aqueous ammonia (50:8:1) Rf 0.07.

Example 12

3-[2-(Dimethylamino)ethyl]-N-[2-[3-[(methylsulphonyl)amino]phenyl]ethyl]-1H-indole-5-carboxamide oxalate

(i) *3-[2-(Dimethylamino)ethyl]-N-[2-(3-nitrophenyl)ethyl]-1H-indole-5-carboxamide*

A suspension of 3-[(2-dimethylamino)ethyl]-1*H*-indole-5-carboxylic acid (0.15g) in anhydrous pyridine (7ml) at −12° (cooling bath temperature) was treated with thionyl chloride (0.052ml) and stirred at about −12° for 0.5h. The resultant mixture was allowed to warm up to about 0° over a period of 1.5h. The suspension was re-cooled to about −12° and treated with a solution of *m*-nitrophenethylamine (0.107g) in anhydrous pyridine (1ml). After stirring at −12° for 0.5h the resultant solution was allowed to reach room temperature over a period of 1.5h and was then stirred at room temperature for 18h. Two further portions of thionyl chloride (0.02ml and 0.052ml) were added at about −12° during a period of 4h. Stirring was then continued at room temperature for 3 days. The solvent was removed by rotary evaporation and the residue purified by flash chromatography eluting with dichloromethane-ethanol-0.88 aqueous ammonia (100:8:1). Rotary evaporation of the appropriate fractions gave the title compound as a gum (0.4g).

T.l.c. Silica, Dichloromethane-ethanol-0.88 aqueous ammonia (100:8:1) Rf 0.2 uv/IPA

(ii) *N-[2-(3-Aminophenyl)ethyl]-3-(2-dimethylaminoethyl)-1H-indole-5-carboxamide dihydrochloride*

A solution of the product of Stage (i) (0.26g) in ethanol (15ml) was hydrogenated in the presence of 10% palladium oxide on carbon (0.4g of a 50% paste in water, pre-reduced in ethanol (15ml) until uptake of hydrogen had ceased. The catalyst and solvent were removed to yield a gum (0.3g) which was purified by flash chromatography eluting with dichloromethane-ethanol-0.88 aqueous ammonia (50:8:1). Rotary evaporation of the appropriate fractions gave the free base as a foam (0.13g).

T.l.c. Silica, Dichloromethane-ethanol-0.88 aqueous ammonia (25:8:1) Rf 0.6. Detection: uv/IPA

A solution of the free base (0.12g) in ethanol (10ml) was treated with excess ethereal hydrogen chloride and the resultant solution was evaporated to dryness to give the *title compound* as a hygroscopic foam (0.115g).

T.l.c. Silica, Dichloromethane-ethaol-0.88 aqueous ammonia (25:8:1) Rf 0.6. Detection: uv/IPA

(iii) *3-[2-(Dimethylamino)ethyl]-N-[2-[3-[(methylsulphonyl)amino]phenyl]ethyl]-1H-indole-5-carboxamide oxalate (1:1)*

A stirred, cold (−15°) solution of the free base of the product of Stage (ii) (0.23g) in anhydrous pyridine (9ml) was treated with methanesulphonyl chloride (0.05ml) and the resultant solution allowed to reach room temperature over a period of about 2h. After stirring at room temperature for about 24h the solution was cooled to approximately 11° and treated with further methanesulphonyl chloride (0.05ml) and stirring continued at room temperature for 20h. The solvent was removed by rotary evaporation and the residual gum purified by flash chromatography eluting with dichloromethane-ethanol-0.88 aqueous ammonia (50:8:1). Rotary evaporation of the appropriate fractions gave the *title compound* free based as a gum (0.155g).

T.l.c. Silica, Dichloromethane-ethanol-0.88 aqueous ammonia (25:8:1) Rf 0.6 u.v./IPA.

A hot solution of the free base (0.155g) in absolute alcohol (2ml) was treated with a hot solution of oxalic acid (0.0325g) in hot absolute alcohol (2ml). Methanol (5ml) was added to re-dissolve the precipitated gummy salt. Rotary evaporation of the solvent gave the *title compound* as a foam. (0.12g) m.p. 140–150° (shrinks at 80°)
T.l.c. Silica, Dichloromethane-ethanol-0.88 aqueous ammonia (25:8:1) Rf 0.6 u.v./IPA.

Assay Found: C,55.1; H,5.9; N,10.5;
$C_{22}H_{28}N_4O_3S.C_2H_2O_4$ 0.1 H_2O requires C,55.4; H,5.8; N,10.8%.

The following example illustrates a pharmaceutical formulation according to the invention containing 3-(2-Aminoethyl)-N-[2-[4-(dimethylamino)phenyl]ethyl]-1*H*-indole-5-carboxamide dihydrochloride as the active ingredient. Other compounds of the invention may be formulated in a similar manner.

Tablets for Oral Administration

	mg/tablet
Active Ingredient	10
Magnesium Stearate BP	0.5
Anhydrous Lactose	99

The active ingredient is sieved and blended with the anhydrous lactose and magnesium stearate. The mix is then compressed into tablets using a Manasty F_3 tablet machine fitted with 8.0mm concave punches.

Injection for Intravenous Administration

	mg/ml
Active Ingredient	0.6mg
Sodium Chloride BP	as required
Water for Injection BP	1.0ml

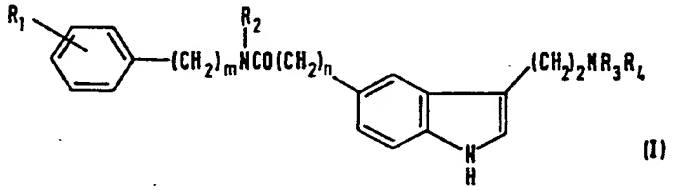
Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or to facilitate solution of the active ingredient. Alternatively suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles.

Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

CLAIMS

1. Compounds of the general formula (I):



(I)

where

R_1 represents a group R_5R_6N–, a group $R_5O_2C(CH_2)_p$–, a group $R_5R_6NCO(CH_2)_p$–, a group $R_5CONH(CH_2)_p$–, a group $R_5R_6NSO_2(CH_2)_p$– or a group $R_7SO_2NH(CH_2)_p$–, (where R_5 and R_6, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group, or R_5 and R_6 together with the nitrogen atom to which they are attached form a saturated monocyclic 5- to 7-membered ring; R_7 represents a C_{1-3} alkyl group and p is zero or one); R_2 represents a hydrogen atom or a C_{1-3} alkyl group, R_3 and R_4 which may be the same or different each represents a hydrogen atom, a C_{1-3} alkyl group, or a 2-propenyl group; m is zero or an integer from 1 to 4; and n is zero or one (with the proviso that m and n are not both zero); and physiologically acceptable salts and solvates thereof.

2. Compounds according to claim 1, wherein R_1 represents a group R_5R_6N–, $R_5O_2C(CH_2)_p$–, $R_5R_6NCO(CH_2)_p$–, $R_5CONH(CH_2)_p$–, $R_5R_6NSO_2(CH_2)_p$– or a group $R_7SO_2NH(CH_2)_p$ where R_5 and R_6, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group.

3. Compounds according to claim 1, wherein R_1 represents a R_5R_6N–, $R_5O_2C(CH_2)_p$–, $R_5R_6NCO(CH_2)_p$–, $R_5CONH(CH_2)_p$– or $R_5R_6NSO_2(CH_2)_p$– group where R_5 and R_6, which may be the same or different, each represents a hydrogen atom or a methyl group.

4. Compounds according to claim 1, wherein R_1 represents a group selected from H_2NCOCH_2–, CH_3SO_2NH–, H_2NCO–, $(CH_3)_2N$–, CH_3O_2C–, pyrrolidino and $CH_3NHSO_2CH_2$–.

5. Compounds according to any of claims 1 to 4, wherein R_2 represents a hydrogen atom or a methyl group.

6. Compounds according to any of claims 1 to 5, wherein m is 2.

7. Compounds according to any of claims 1 to 6, wherein R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group.

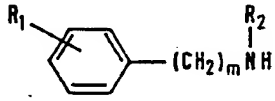
8. Compounds according to claim 1, wherein R_2 represents a hydrogen atom; R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a methyl group; m represents an integer 2; R_1 represents the group H_2NCOCH_2–, CH_3SO_2NH–, CH_3CONH–, H_2NCO–, $(CH_3)_2N$–, CH_3O_2C–, $CH_3NHSO_2CH_2$– or a pyrrolidino ring; and the substituent R_1 on the phenyl ring is at the meta or para position.

9. Compounds according to claim 8 wherein R_1 represents the group $(CH_3)_2N$–, CH_3O_2C–, H_2NCOCH_2– or CH_3CONH– and the group R_1 is at the para position.

10. 3-(2-Aminoethyl)-N-[2-[4-(dimethylamino)phenyl]ethyl]-1*H*-indole-5-carboxamide;
methyl 4-[2-[[[3-(2-aminoethykl)-1*H*-indol-5-yl]carbonyl]amino]ethyl]benzoate;
and physiologically acceptable salts and solvates thereof.

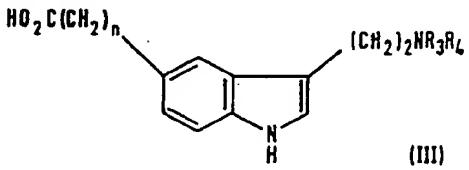
11. A pharmaceutical composition which comprises at least one compound of formula (I) as defined in any of claims 1 to 10 or a physiologically acceptable salt or solvate thereof together with one or more physiologically acceptable carriers or diluents.

12. A process for the preparation of a compound of general formula (I) as defined in any of claims 1 to 10, or a physiologically acceptable salt or solvate thereof, which comprises:
(A) condensing an amine of general formula (II):



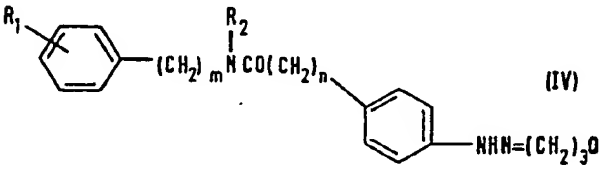
(II)

with an acid of general formula (III):



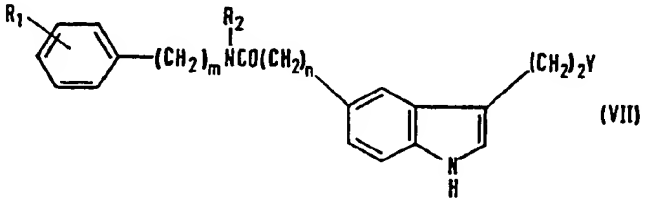
(III)

or an acylating agent corresponding thereto, or a salt or a protected derivative thereof; or
(B) cyclising a compound of general formula (IV):



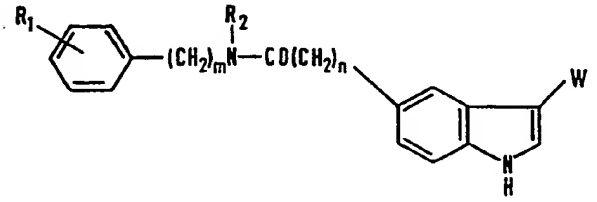
(IV)

wherein Q is the group NR_3R_4 (or a protected derivative thereof) or a leaving atom or group; or
(C) reacting a compound of general formula (VII):



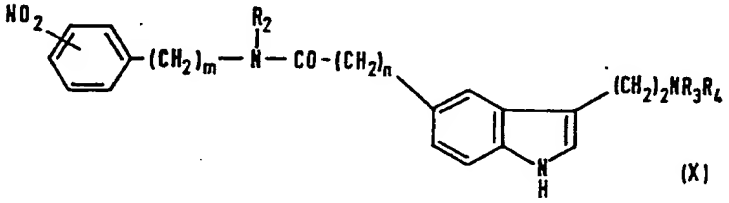
(VII)

(wherein Y is a readily displaceable group) or a protected derivative thereof, with an amine of formula R_3R_4NH; or
(D) reducing a compound of general formula (VIII):



(VIII)

(wherein W is a group capable of being reduced to give the required $-(CH_2)_2NR_3R_4$ group or to give a protected derivative of $-(CH_2)_2NR_3R_4$) or a salt or protected derivative thereof; or
(E) for the production of a compound of general formula (I) subjecting another compound of general formula (I) or a salt or protected derivative thereof to an interconversion reaction; or
(F) for the production of a compound of general formula (I) wherein R_1 represents H_2N-, reducing a compound of general formula (X):



; or

(X)

(G) subjecting a protected derivative of a compound of general formula (I) or a salt thereof to reaction to remove one or more protecting groups; and if necessary or desired subjecting the compound resulting from any of steps (A) to (F) to one or two further reactions comprising
(H) (i) removing any protecting groups; and (ii) converting a compound of general formula (I) or a salt thereof into a physioligically acceptable salt or solvate thereof.

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